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Use Rate and Outcome in Bilateral Internal Thoracic Artery Grafting: Insights From a Systematic Review and Meta-Analysis

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***Background*—**This meta-analysis was designed to assess whether center experience affects the short- and long-term results and the relative benefits of bilateral internal thoracic artery grafting (BITA) for coronary artery bypass grafting.

***Methods and Results*—**MEDLINE and EMBASE were searched to identify all articles reporting the outcome of BITA in patients undergoing coronary artery bypass grafting. The BITA center experience was gauged according to the percentage use of BITA in the institutional overall coronary artery bypass grafting population (%BITA). The primary outcome was long-term all-cause mortality. Secondary outcomes were operative mortality, perioperative myocardial infarction, perioperative stroke, deep sternal wound infections (DSWIs), and major postoperative adverse event. The rates of the primary and secondary outcomes were calculated after adjusting for %BITA. Primary and secondary outcomes were also compared between the BITA and the single internal thoracic artery arms in the adjusted studies. Meta-regression was used to evaluate the effect of %BITA on the primary and secondary outcomes. Thirty-four studies (27 894 patients undergoing BITA) were included. In the pooled analysis, the incidence rate for long-term mortality was 2.83% (95% confidence interval, 2.21%–3.61%). %BITA was significantly and inversely associated with long-term mortality and the rate of DSWI. In the pairwise comparison, %BITA was significantly and inversely associated with the risk of long-term mortality and DSWI in the group undergoing BITA.

***Conclusions*—**BITA series with higher %BITA report significantly lower long-term mortality and DSWI rate as well as higher long-term survival advantage and lower relative risk of DSWI in their BITA cohort. These findings suggest that a specific volume-outcome relationship exists for BITA grafting. **(*J Am Heart Assoc*. 2018;7:e009361. DOI: 10.1161/JAHA.118.009361.)**

Key Words: bilateral internal thoracic artery • CABG • coronary artery bypass graft • coronary artery bypass graft surgery • experience • meta-analysis

The relationship between center or operator experience and outcome has extensively been described in medicine and in surgery.[1] The volume/outcome (V/O) effect is particularly evident for technically complex procedures, such as off-pump surgery or valve repair procedures.[2] This has resulted in recommendations for minimum center- and surgeon-specific procedural volumes, as well as for specialized referral centers for highly complex cardiovascular and cancer operations.[1]

Coronary artery bypass grafting surgery (CABG) is the most common cardiac surgical procedure performed worldwide, and a V/O effect for CABG has been extensively described.[1,3]

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Accompanying Tables S1 through S3 and Figures S1 through S5 are available at http://jaha.ahajournals.org/content/7/11/e009361/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Our analysis suggests the existence of a use rate to outcome effect for bilateral internal thoracic artery grafting.

What Are the Clinical Implications?

- Our findings suggest the possibility that the creation of specialized tertiary centers for coronary surgery, similar to those that exist for aortic surgery and transplantation, may improve the outcomes of bilateral internal thoracic artery grafting.

The use of bilateral internal thoracic artery (BITA) increases the technical complexity of the CABG operation.[4] Previously published studies on the V/O effect in CABG did not stratify the results according to the type of technique used, although in the great majority of the published series, BITA was used only in a small minority of patients.

We hypothesized that, because of the more complex nature of the procedure, a specific center experience to outcome relationship exists for BITA grafting; therefore, we aimed at investigating this by using a meta-analytic approach.

Methods

We conducted this systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[5] Table S1 illustrates the Meta-Analysis of Observational Studies in Epidemiology guidelines checklist. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Search Strategy and Study Selection Criteria

OVID versions of MEDLINE and EMBASE were searched from January 1972 to June 2017 to identify all articles reporting the outcome of BITA in patients undergoing CABG.

The following keywords were used: "bilateral," "double," "mammary," "thoracic," "artery," "multiple," "total," "arterial," "revascularization," and "coronary." Their combinations were searched using the term "AND." All citations were screened for study inclusion independently by 2 investigators (A.D.F and M.G.). In case of disagreement, a consensus was reached. In addition, the bibliography of all studies and meta-analyses was searched to identify further publications (backward snowballing).

Inclusion criteria for analysis were single-institution study, sample size of at least 100 patients, and English language. We excluded studies in which the percentage of BITA use of the individual center (number of patients undergoing BITA/total number of patients undergoing CABG in the center in the study period=%BITA) could not be extracted. In case of overlapping between studies or multiple publications from the same center, only the publication with the largest sample size was included.

The critical appraisal of the quality of included studies was assessed using the Newcastle-Ottawa Scale for observational studies.[6] The highest possible score is 9 stars; <6 stars was considered low quality, whereas ≥6 stars was considered high quality (Table S2).

Data Abstraction

The following data were abstracted: study period, country, institution, total sample size, number of patients undergoing BITA, %BITA, annual CABG volume of the individual center (total number of CABGs in the study/the study period), study design, and follow-up duration. The following patient characteristics were abstracted: age, female sex, diabetes mellitus, left ventricular ejection fraction, number of grafts per patient, number of internal thoracic artery grafts per patient, use of internal thoracic artery sequentials, use of skeletonization technique for BITA harvesting, and chronic obstructive pulmonary disease.

For descriptive purposes, the studies were divided according to quartiles of %BITA (boundaries for the quartiles were 17.1%, 29.2%, and 50.3%; the range of %BITA was 3.7%–64%). In all the other analysis, %BITA was analyzed as a continuous variable.

For the BITA versus single internal thoracic artery (SITA) comparison, data were abstracted from the adjusted series only (covariate adjusted or propensity matched). Crude event rates, unadjusted and adjusted hazard ratios, 95% confidence intervals (CIs) for BITA and SITA, and log p-rank values were abstracted. For the secondary outcomes, number of events was extracted for each outcome.

Continuous variables were expressed as median (25th–75th percentile) or as mean±SD. Categorical variables were reported as frequency (percentage).

Outcomes

The primary outcome was long-term all-cause mortality.

The secondary outcomes were operative mortality, perioperative myocardial infarction, perioperative stroke, deep sternal wound infections (DSWIs), and major postoperative adverse events, defined as the composite of operative mortality, perioperative myocardial infarction, perioperative stroke, and DSWIs. Major postoperative adverse event was derived only from studies that reported all 4 individual outcome components.

Analytic Plan and Statistical Analysis

In the pooled analyses, the incident rate or the pooled event rates (PERs) of the primary and secondary outcomes in the BITA series were calculated according to the %BITA.

In the pairwise comparisons including only the adjusted studies, the relative risks of the primary and secondary outcomes in the BITA series were calculated according to the %BITA.

Pooled analysis

To account for the differential follow-up times of the primary outcome in the various studies, an underlying Poisson process with a constant event rate was assumed with a total number of events observed within a treatment group of the total person-time of follow-up for that treatment group calculated from study follow-up. A log-link function was used to model the incidence rate (IR), and a random effect was used. When the number of events was not available from text or tables, the number of events was derived from the unadjusted Kaplan-Meier curves using GetData Graph Digitizer software 2.26 (http://getdata-graph-digitizer.com) using a previously described method.[7]

For secondary outcomes, the PERs with 95% CIs were calculated.

BITA versus SITA comparison

For the primary outcome, the generic inverse variance (DerSimonian-Laird) method was used to pool the natural logarithm of the IR ratio across studies to account for potentially different follow-up durations between the studies. We estimated the IR ratio through several means, depending on the available study data. When hazard ratios were provided, we took the natural logarithm of the hazard ratio; the standard error was derived from the 95% CI or log-rank *P* value.[8] When event rates were not readily available, they were extracted from Kaplan-Meier curves.[7,9] The standard error was estimated from the number of events in each arm.[8] For secondary outcomes, individual and pooled odds ratio (OR) with 95% CIs were used.

Meta-regression

In the pooled and pairwise analysis, univariable meta-regression was used to explore the association between % BITA and the primary and secondary outcomes.

A mixed-effects meta-regression model that contained both study-specific covariates and random-effect components was used to allow for the division of heterogeneity into an explained (by the covariates) and an unexplained (the random-effects) component.[10] Each study was weighted by the inverse of the variance of the estimate for that study, and between-study variance was estimated with DerSimonian-Laird estimator.

In both sets of analyses, a multivariable meta-regression model was used to assess the association between %BITA with the primary outcome while also adjusting for age, sex, diabetes mellitus, and annual CABG hospital volume. A separate multivariable meta-regression model, including % BITA, sex, diabetes mellitus, annual CABG volume, and skeletonization, was used to assess for the analysis of DSWI.

The Cochran Q statistic and the I^2 test were used to assess studies' heterogeneity. For the primary outcome, if significant heterogeneity was detected (I^2>75%), a leave-one-out sensitivity analysis was performed to assess for single comparison driven inference. Funnel plots and Egger regression test were used to assess for potential publication bias. If publication bias was suspected, visual assessment of the cumulative forest plot and Duval and Tweedie's trim and fill methods were used for further assessment.

A random-effect model (inverse variance method)[11] was used for all the analysis. Hypothesis testing for equivalence was set at the 2-tailed 0.05 level.

All analyses were performed using R, version 3.3.3 (R Project for Statistical Computing) using the following statistical packages: "meta" and "metafor"[12,13] within the RStudio, 0.99.489 (http://www.rstudio.com) and Comprehensive Meta-Analysis V 3.0 (2006; Biostat, Inc, Englewood, NJ).

Results

Literature Search

The literature search identified 2899 potentially eligible studies. Twenty-two additional articles were identified through backward snowballing. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram is reported in Figure 1.

Studies' and Participants' Characteristics

A total of 34 studies including 27 894 patients who had CABG using BITA were included.[14–47] Details of the individual studies are shown in Tables 1 and 2 and Table S3. The weighted mean follow-up time was 7.7±1.2 years. For the pairwise comparison, 27 adjusted studies (12 propensity matched) were included (75 334 patients; 19 290 BITAs and 56 044 SITAs). Eight studies (13 292 patients) were included in the analysis of the composite major postoperative adverse event.

The included studies were published from 1989 to 2016, and the sample size ranged from 147 to 17 609.

Primary outcome

In the pooled analysis, the IR for long-term mortality in the overall population was 2.83%/year (95% CI, 2.21%/year–

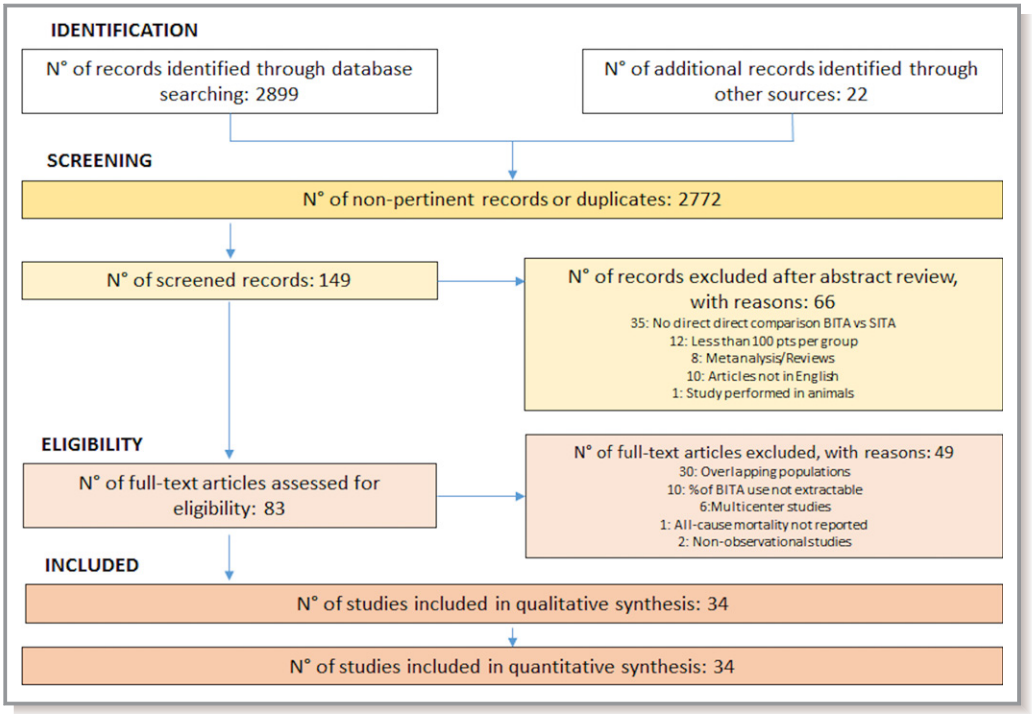


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart. BITA indicates bilateral internal thoracic artery; SITA, single internal thoracic artery.

3.61%/year; Table 3). The leave-one-out analysis is shown in Figure S1, and the funnel plot and the cumulative analysis are shown in Figure S2. %BITA was significantly and inversely associated with long-term mortality in the univariable meta-regression (β=−0.02, *P*=0.02; Figure 2A) and the multivariable meta-regression (β=−0.03, *P*=0.04; Figure 2B).

In the pairwise comparison with SITA, the use of BITA was associated with a significantly lower long-term mortality (IR ratio, 0.78; 95% CI, 0.72–0.84; Figure S3). %BITA was significantly and inversely associated with the IR ratio for long-term mortality in both the univariable meta-regression (β=−0.006, *P*=0.01; Figure 3A) and the multivariable meta-regression (β=−0.008, *P*=0.03; Figure 3B).

Secondary outcomes

In the pooled analysis, the PER for operative mortality was 1.6% (95% CI, 1.2%–2.2%), the PER for myocardial infarction was 1.6% (95% CI, 1.1%–2.4%), the PER for perioperative stroke was 1.1% (95% CI, 0.9%–1.4%), the PER for DSWI was 2.2% (95% CI, 1.7%–2.7%), and the PER for major postoperative adverse event was 5.7% (95% CI, 4.7%–6.8%) (Table 3). %BITA was significantly and inversely associated with DSWI, according to the univariable and multivariable meta-regressions (β=−0.001 [*P*=0.006] and β=−0.02 [*P*<0.001], respectively; Table 3 and Figure 4). %BITA did not influence the other secondary outcomes (Table 3 and Figure S4).

In the pairwise comparison with SITA, BITA use was associated with a significantly higher incidence of DSWI (OR, 1.58; 95% CI, 1.15–2.19) and a significantly lower rate of perioperative stroke (OR, 0.76; 95% CI, 0.61–0.94). %BITA was significantly and inversely associated with the OR for DSWI by univariable and multivariable meta-regressions (β=−0.020 [*P*=0.02] and β=−0.03 [*P*=0.005], respectively; Figure 5).

No significant differences were found for the other secondary outcomes (Figure S5).

Discussion

An inverse relationship between hospital volume and clinical outcome has been described extensively in surgery.[1] Some data suggest that the V/O relationship can be more evident for more complex procedures, such as off-pump CABG, or higher-risk patients.[2]

The V/O effect in CABG has been the focus of a large amount of research. Despite controversy related to the methodological quality of the sources used in the published studies and the lack of a clear-cut explanation, it is usually accepted that hospitals that perform a high annual volume of CABG and have more experience with the procedure have better outcomes than hospitals that perform a smaller number of procedures.[1–3] The use of BITA during CABG adds technical complexity to the operation. In a survey of all UK consultant cardiac surgeons, the perceived increased technical difficulty and need of a learning curve were the most frequent reason to explain the low adoption rate of BITA.[4]

Table 1. Overview of the Included Studies: 1

Study	Year	Center	Study Period	Setting	Type of Study
Benedetto et al[14]	2014	Harefield Hospital (London, UK)	2001–2013	First-time isolated CABG	Retrospective
Buxton et al[15]	1998	Austin and Repatriation Medical Center, University of Melbourne (Melbourne, Victoria, Australia)	1985–1995	Isolated primary CABG	Retrospective
Calafiore et al[16]	2004	University Hospital (Torino, Italy) and "G D'Annunzio" University (Chieti, Italy)	1986–1999	Patients <75 y who undergo first myocardial revascularization	Retrospective
Carrier et al[17]	2009	Montreal Heart Institute (Montreal, Quebec, Canada)	1995–2007	Isolated primary CABG	Retrospective
Danzer et al[18]	2001	University Hospital (Geneva, Switzerland)	1983–1989	Isolated primary CABG	Retrospective
Dewar et al[19]	1995	Vancouver Hospital and Health Sciences Centre, University of British Columbia (Vancouver, British Columbia, Canada)	1984–1992	Isolated primary CABG (93.2% were having a first operative procedure)	Retrospective
Elmistekawy et al[20]	2012	Ottawa Heart Institute (Ottawa, Ontario, Canada)	1997–2007	Isolated CABG in patients ≥65 y	Retrospective
Endo et al[21]	2001	Tokyo Women's Medical University (Tokyo, Japan)	1985–1998	Elective isolated primary CABG (including children with Kawasaki disease)	Retrospective
Gansera et al[22]	2001	Klinikum Bogenhausen (Munich, Germany)	1996–1999	Isolated CABG	Retrospective
Gansera et al[23]	2004	Klinikum Bogenhausen (Munich, Germany)	1997–1999	Elective isolated primary CABG	Retrospective
Grau et al[24]	2015	The Valley Columbia Heart Center, Columbia University College of Physicians and Surgeons (Ridgewood, NJ)	1994–2013	Isolated CABG	Retrospective
Hirotani et al[25]	2003	Tokyo Saiseikai Central Hospital (Minato-Ku, Tokyo, Japan)	1991–2003	Isolated primary CABG in diabetic patients	Retrospective
Ioannidis et al[26]	2001	St Luke's–Roosevelt Hospital Center (New York, NY)	1993–1996	Isolated CABG	Prospective
Itoh et al[27]	2016	Saitama Medical Center, Jichi Medical University (Saitama, Japan)	1990–2014	Isolated CABG in elderly patients (≥75 y)	Retrospective
Johnson et al[28]	1989	Milwaukee Heart Surgery Associates, SC, and St Mary's Hospital (Milwaukee, WI)	1972–1986	Isolated CABG (including redo)	Retrospective
Jones et al[29]	2000	Baylor College of Medicine and Veterans Affairs Medical Center (Houston, TX)	1986–1996	Isolated primary CABG in patients >65 y	Retrospective
Joo et al[30]	2012	Yonsei Cardiovascular Hospital (Seoul, Republic of Korea)	2000–2009	Isolated OPCAB	Retrospective
Kelly et al[31]	2012	Queen Elizabeth II Health Sciences Center (Halifax, Nova Scotia, Canada)	1995–2009	Isolated primary CABG	Retrospective
Kinoshita et al[32]	2015	Shiga University of Medical Science (Otsu, Japan)	2002–2014	Isolated CABG (patients stratified by GFR)	Retrospective

Continued

Table 1. Continued

Study	Year	Center	Study Period	Setting	Type of Study
Konstanty et al[33]	2012	Collegium Medicum Jagiellonian University (Krakow, Poland)	2006–2008	Isolated primary CABG in diabetic patients	Retrospective
Kurlansky et al[34]	2010	Florida Heart Research Institute (Miami, FL)	1972–1994	Isolated CABG	Retrospective
Locker et al[35]	2012	Mayo Clinic (Rochester, MN)	1993–2009	Isolated primary CABG	Retrospective
Lytle et al[36]	2004	The Cleveland Clinic Foundation (Cleveland, OH)	1971–1989	Isolated primary CABG	Retrospective
Medalion et al[37]	2015	Tel Aviv Sourasky Medical Center (Tel Aviv, Israel)	1996–2008	Isolated CABG in patients ≥70 y	Retrospective
Mohammadi et al[38]	2014	Quebec Heart and Lung Institute (Quebec City, Quebec, Canada)	1991–2011	Isolated primary CABG in patients with EF ≤40%	Retrospective
Naunheim et al[39]	1992	St Louis University Medical Center (St Louis, MO)	1972–1975	Isolated CABG	Retrospective
Navia et al[40]	2016	Instituto Cardiovascular de Buenos Aires (Buenos Aires, Argentina)	1996–2014	Isolated urgent or elective CABG (BITA grafting in a T configuration)	Retrospective
Parsa et al[41]	2013	Duke University Medical Center (Durham, NC)	1984–2009	Isolated CABG	Prospective
Pettinari et al[42]	2014	Ziekenhuis Oost Limburg (Genk, Belgium) and University Hospitals Leuven (Leuven, Belgium)	1972–2006	CABG in elderly patients (≥70 y)	Retrospective
Pusca et al[43]	2008	Emory University School of Medicine (Atlanta, GA)	1997–2006	Isolated CABG	Retrospective
Rosenblum et al[44]	2016	Emory University School of Medicine (Atlanta, GA)	2003–2013	Primary isolated CABG	Retrospective
Stevens et al[45]	2004	Montreal Heart Institute (Montreal, Quebec, Canada)	1985–1995	Isolated primary CABG with ≥3 grafts	Retrospective
Tarelli et al[46]	2001	Varese Hospital (Varese, Italy)	1988–1990	Isolated CABG	Retrospective
Walkes et al[47]	2002	Baylor College of Medicine and Veterans Affairs Medical center (Houston, TX)	1990–2000	Isolated CABG	Retrospective

BITA indicates bilateral internal thoracic artery; CABG, coronary artery bypass grafting; EF, ejection fraction; GFR, glomerular filtration rate; OPCAB, off-pump coronary artery bypass.

In the recently published ART (Arterial Revascularization Trial), only 83.6% of the patients randomized to BITA received the assigned treatment (versus 96.1% in the conventional CABG group).[48] This high crossover rate in the BITA series is a testament to higher technical complexity of the operation, and it is even more meaningful if one considers that only expert BITA surgeons were allowed to participate in ART. However, it also raises the possibility that the BITA surgeons were not all equally experienced in BITA grafting because the crossover rate varied from 0% to 42.9% on a center level and from 0% to 100% for the 168 participating surgeons, suggesting the need for appropriate and documented experience for participation in trials involving complex technical procedures. Thus, as complexity of the coronary surgery increases with the addition of a BITA grafting strategy, institution experience with BITA may play an ever-increasing role on outcomes. However, to date, this subject has not been investigated in detail.

Our data suggest that a relationship between the rate of BITA use at the center level and the clinical results exists at least for the 2 most important outcomes associated with BITA grafting: long-term survival and incidence of DSWI. In our analysis, long-term mortality was significantly and inversely associated with %BITA, with better survival reported by centers with high %BITA. In the pairwise comparison with SITA, the long-term survival benefit associated with the use of BITA was significantly associated with %BITA, with centers with high %BITA reporting a significantly larger survival advantage for patients undergoing BITA. The effect of %BITA on long-term mortality remained significant even when entering the annual hospital volume as a covariate in the

Table 2. Overview of the Included Studies: 2

Study	Overall Population, n	BITA, n	Mean/Median Follow-Up, y	Completeness of Follow-Up, %
Benedetto et al[14]	4195	750	4.8±3.2 (PSM sample)	100
Buxton et al[15]	2826	1269	4.3	95.9
Calafiore et al[16]	1602	1026	BITA: 7.1±5.0	100
Carrier et al[17]	6655	1235	10	99
Danzer et al[18]	521	382	10	97.5
Dewar et al[19]	1142	377	4	NR
Elmistekawy et al[20]	3940	359	NR	NR
Endo et al[21]	1131	443	6.2	99.3
Gansera et al (2001)[22]	3671	1487	NR	NR
Gansera et al (2004)[23]	1378	716	5.3	NR
Grau et al[24]	6666	1544	BITA: 10.9±5	100
Hirotani et al[25]	303	179	NR	95
Ioannidis et al[26]	1697	867	NR	NR
Itoh et al[27]	400	107	9.0±5.8	95.6
Johnson et al[28]	2014	576	NR	100
Jones et al[29]	510	172	5.0±3.1	100
Joo et al[30]	1749	392	BITA: 6.9±2.1	98.1
Kelly et al[31]	7633	1079	BITA: 5.4	NR
Kinoshita et al[32]	1203	750	PSM BITA: 5.6±3.3	99
Konstanty et al[33]	147	38	NR	NR
Kurlansky et al[34]	4584	2215	BITA: 12.7	BITA: 96.7
Locker et al[35]	8295	860	7.6±4.6	100
Lytle et al[36]	10 124	2001	BITA: 16.2±2.4	100
Medalion et al[37]	1627	1045	8.2±4.5	98
Mohammadi et al[38]	1795	129	PSM BITA: 8.6±5.1	92.7
Naunheim et al[39]	365	100	NR	96.5
Navia et al[40]	2486	2098	Median, 5.5 (IQR, 2.6–8.8)	95
Parsa et al[41]	17 609	728	NR	100
Pettinari et al[42]	3496	1328	3.1	100
Pusca et al[43]	10 811	599	NR	NR
Rosenblum et al[44]	8254	873	Median, 2.8 (IQR, 1.1–4.9)	100
Stevens et al[45]	4382	1835	BITA: 8±2	98
Tarelli et al[46]	300	150	BITA: 9.2±2.8	100
Walkes et al[47]	1069	158	NR	NR

BITA indicates bilateral internal thoracic artery; IQR, interquartile range; NR, not reported; PSM, propensity score matched.

meta-regression model, suggesting the existence of an "experience effect" specific for BITA grafting and independent from the V/O relationship for standard CABG.

The rate of DSWI and the increase in the risk of DSWI in the BITA group were also significantly and inversely associated with %BITA. Centers with high %BITA reported a lower incidence of DSWI in the BITA series and a lower relative risk of DSWI in the BITA group compared with the SITA series. Furthermore, the incidence and risk of the short-term outcomes, such as operative mortality, perioperative myocardial infarction, and perioperative stroke, were not influenced by the %BITA.

Taken together, our findings seem to suggest that the reasons for the reported difference in outcomes between

Table 3. Outcomes Summary

Quartile	No. of Studies	Patients	PER/IR, %	95% CI, %	Heterogeneity, I^2, *P* Value	τ^2
Long-term mortality						
First quartile	5	3377	3.68	2.18–6.21	98.40, *P*<0.001	0.336
Second quartile	8	4579	3.2	2.35–4.37	96.52, *P*<0.001	0.185
Third quartile	8	7712	4.45	2.73–7.26	99.40, *P*<0.001	0.485
Fourth quartile	7	3712	1.04	0.50–2.19	97.60, *P*<0.001	0.924
Overall	28	19 380	2.83	2.21–3.61	98.90, *P*<0.001	0.412
Perioperative MI						
First quartile	5	2598	1.2	0.49–2.91	78.972, *P*=0.001	0.778
Second quartile	4	1530	2.121	1.02–4.36	60.970, *P*=0.053	0.329
Third quartile	3	3954	2.454	0.97–6.08	93.294, *P*<0.001	0.643
Fourth quartile	6	5141	1.321	0.72–2.42	81.853, *P*<0.001	0.432
Overall	18	2598	1.632	1.12–2.38	86.706, *P*<0.001	0.546
Stroke						
First quartile	5	2598	1.045	0.64–1.70	27.658, *P*=237	0.086
Second quartile	6	2387	1.27	0.72–2.22	44.368, *P*=110	0.208
Third quartile	4	4846	1.101	0.84–1.44	0.000, *P*=0.530	0
Fourth quartile	7	5891	1.426	0.75–2.70	87.346, *P*<0.001	0.636
Overall	22	15 722	1.142	0.93–1.40	74.605, *P*<0.001	0.36
DSWI						
First quartile	5	3197	2.805	2.17–3.61	0.000, *P*=0.551	0
Second quartile	3	2387	3.304	1.38–7.72	39.075, *P*=0.194	0.5
Third quartile	5	8981	1.525	1.18–1.97	30.744, *P*=0.217	0.164
Fourth quartile	5	6037	1.675	1.28–2.19	0.000, *P*=0.735	0
Overall	18	20 602	1.968	1.70–2.28	46.688, *P*=0.016	0.281
Perioperative mortality						
First quartile	3	2385	1.328	0.45–3.87	88.184, *P*<0.001	0.822
Second quartile	6	3158	1.562	0.65–3.72	82.822, *P*<0.001	0.877
Third quartile	5	5398	1.442	0.89–2.32	74.551, *P*=0.003	0.213
Fourth quartile	5	4845	1.923	1.10–3.34	84.795, *P*<0.001	0.342
Overall	19	15 786	1.591	1.15–2.19	80.805, *P*<0.001	0.352
MAE						
First quartile	2	1232	7.725	3.30–17.03	93.918, *P*<0.001	0.393
Second quartile	2	966	7.122	1.44–28.62	91.912, *P*<0.001	1.314
Third quartile	2	1739	5.474	4.50–6.65	0.000, *P*=0.498	0
Fourth quartile	3	3525	6.632	3.67–11.70	94.552, *P*<0.001	0.282
Overall	9	7462	5.682	4.74–6.79	89.869, *P*<0.001	0.204

IR was used for long-term mortality. CI indicates confidence interval; DSWI, deep sternal wound infection; IR, incidence rate; MAE, major postoperative adverse event (operative mortality+MI+stroke+DSWI); MI, myocardial infarction; PER, pooled event rate.

centers at high and low %BITA are not strictly technical, because outcomes that are heavily influenced by technical factors, such as perioperative myocardial infarction, stroke, and operative mortality, were not significantly associated with %BITA. One explanation for our results may be better patient selection and grafting strategy in centers at high % BITA. It is possible that more experienced centers were more proficient in selecting appropriate patients who

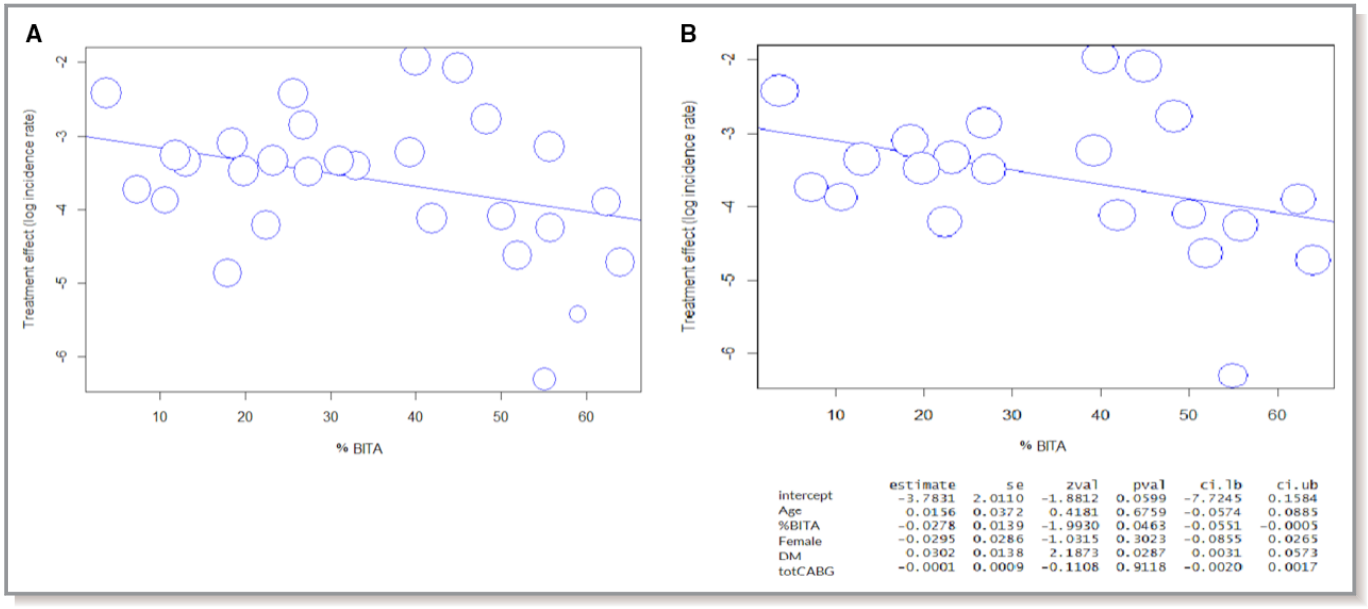


Figure 2. The effect of the percentage of bilateral internal thoracic artery (BITA) use on the long-term mortality (expressed as incidence rate) according to the univariable (A) and multivariable (B) meta-regressions. DM indicates diabetes mellitus; totCABG, total coronary artery bypass grafting.

would benefit from BITA grafting and the use of the arterial grafts.

It is notable that 67% of the studies in the highest quartile of %BITA versus 38% in the lowest quartile used BITA sequentials (P=0.03). It has been shown that an increase in the number of BITA anastomoses is associated with better clinical outcome.[49]

For DSWI, the adoption of the skeletonized technique for harvesting was similar between high and low BITA users (42.9% in the first quartile and 57.1% in the fourth quartile; P=0.56), and the association between the OR for DSWI and % BITA was confirmed, even in the multivariable meta-regression model after adjusting for skeletonization. These results suggest that BITA skeletonization alone is not the explanation for the reported difference in DWSI.

This analysis must be interpreted in the context of some limitations. We used %BITA as opposed to BITA volume as a marker of experience with BITA because we believe that the

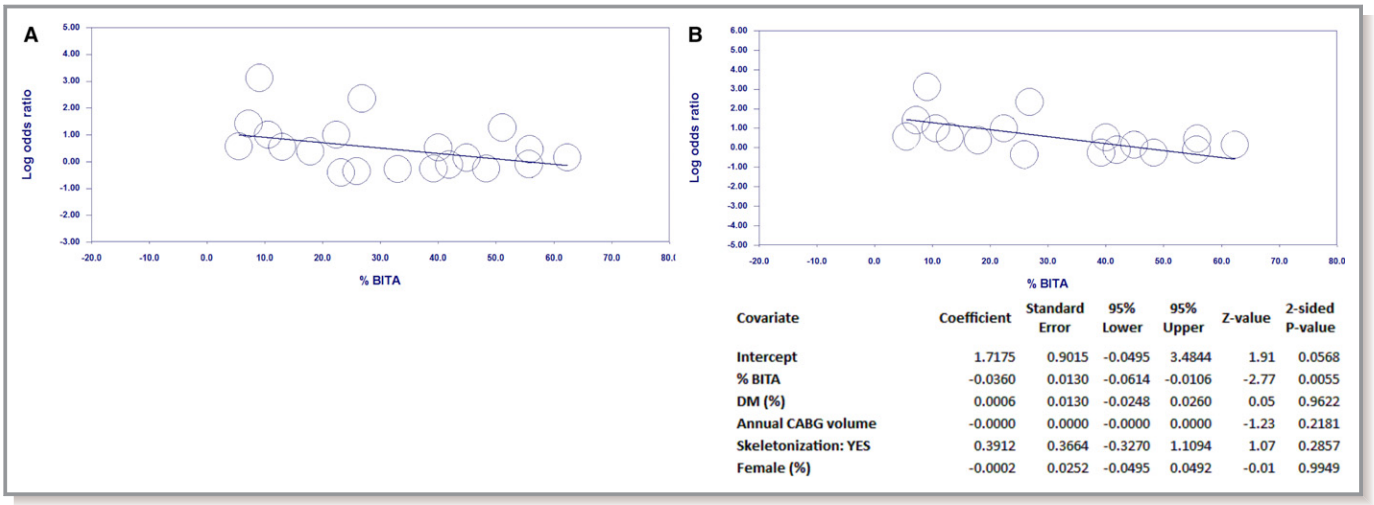
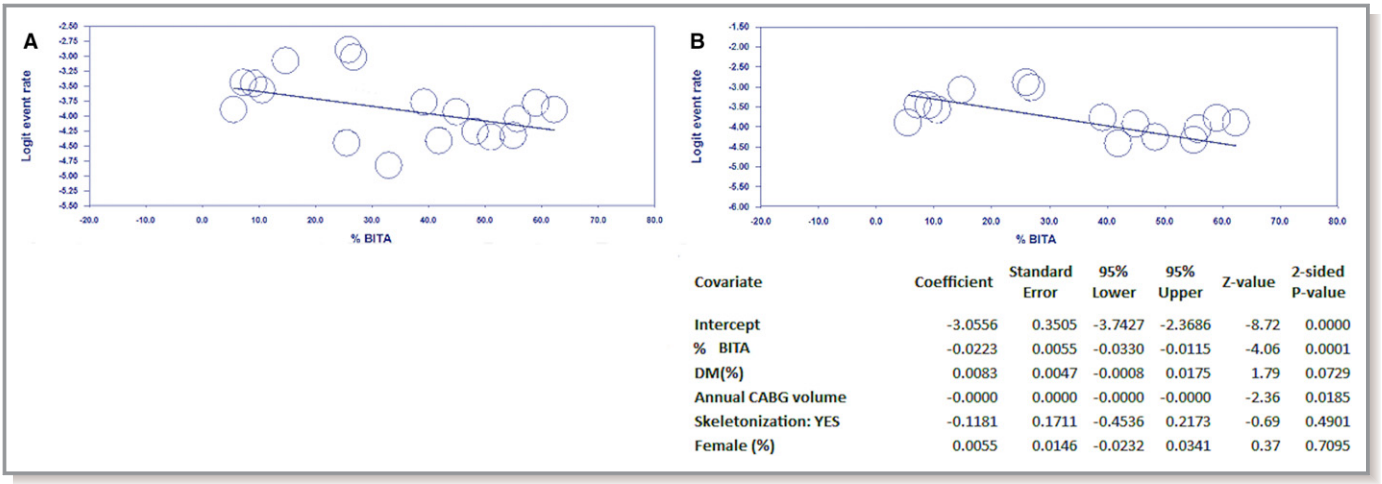


Figure 3. The effect of the percentage of bilateral internal thoracic artery (BITA) use on the long-term mortality (expressed as incident rate ratio) according to the univariable (A) and multivariable (B) meta-regressions. CABG indicates coronary artery bypass grafting; DM, diabetes mellitus.

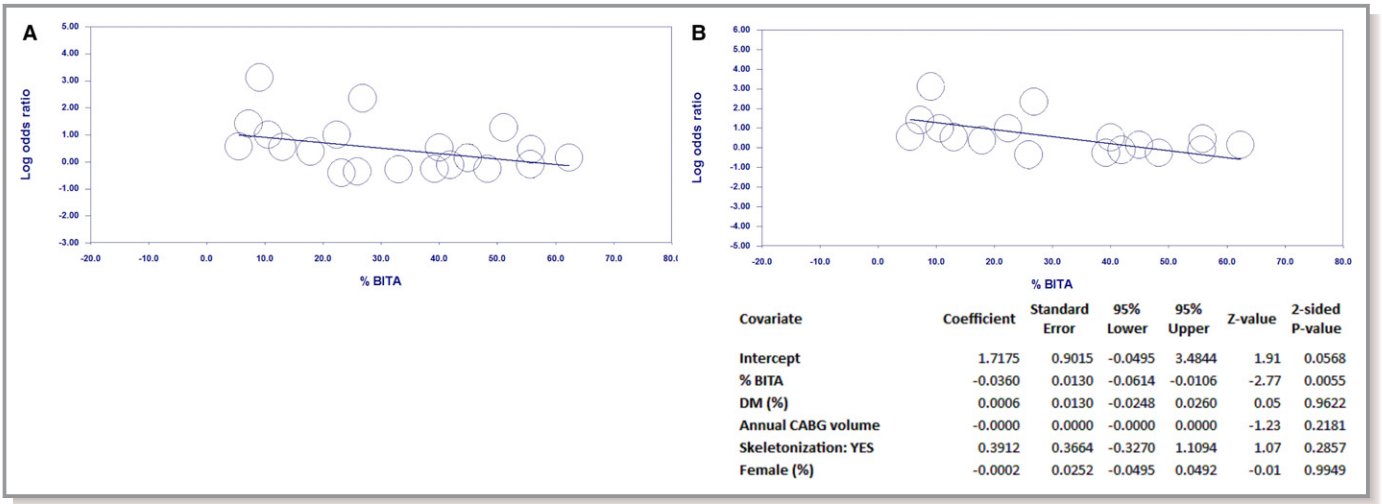


Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	-3.0556	0.3505	-3.7427	-2.3686	-8.72	0.0000
% BITA	-0.0223	0.0055	-0.0330	-0.0115	-4.06	0.0001
DM(%)	0.0083	0.0047	-0.0008	0.0175	1.79	0.0729
Annual CABG volume	-0.0000	0.0000	-0.0000	-0.0000	-2.36	0.0185
Skeletonization: YES	-0.1181	0.1711	-0.4536	0.2173	-0.69	0.4901
Female (%)	0.0055	0.0146	-0.0232	0.0341	0.37	0.7095

Figure 4. The effect of the percentage of bilateral internal thoracic artery (BITA) use on the pooled event rate of deep sternal wound infection by univariable (A) and multivariable (B) meta-regressions. CABG indicates coronary artery bypass grafting; DM, diabetes mellitus.

rate of use is a stronger surrogate measure of familiarity, comfort, and skill in the operation than the absolute volume of procedures performed. However, this assumption is based on the authors' opinion, and has never been objectively validated. We did not capture individual surgeon's experience, which may be more important than center's experience. Also, the included studies used different surgical protocols and definition of outcomes and were in different stages of their BITA learning curve, leading to heterogeneity in the analyzed data. Most important, an unavoidable publication bias exists, because all centers were in some way experienced in the use of BITA (although at different levels). Our analysis probably does not capture the results of inexperienced centers or beginners in BITA grafting who are unlikely to publish their results. In addition, meta-regressions can only be used to assess association and do not infer causality. Nonetheless, despite these limitations, the reproducibility of our results, on the basis of multiple different statistical approaches, supports the robustness of our reported findings.

In conclusion, our analysis suggests the existence of a use rate to outcome effect for BITA grafting. In our study, centers that used BITA more frequently reported a reduced risk of sternal complications and achieved better long-term survival compared with SITA. Our findings suggest the possibility that the creation of specialized tertiary centers for coronary surgery, similar to those that exist for aortic surgery and transplantation, may improve the outcomes of BITA grafting.



Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	1.7175	0.9015	-0.0495	3.4844	1.91	0.0568
% BITA	-0.0360	0.0130	-0.0614	-0.0106	-2.77	0.0055
DM (%)	0.0006	0.0130	-0.0248	0.0260	0.05	0.9622
Annual CABG volume	-0.0000	0.0000	-0.0000	0.0000	-1.23	0.2181
Skeletonization: YES	0.3912	0.3664	-0.3270	1.1094	1.07	0.2857
Female (%)	-0.0002	0.0252	-0.0495	0.0492	-0.01	0.9949

Figure 5. The effect of the percentage of bilateral internal thoracic artery (BITA) use on the odds ratio of deep sternal wound infection by univariable (A) and multivariable (B) meta-regressions. CABG indicates coronary artery bypass grafting; DM, diabetes mellitus.

Disclosures

None.

References

1. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, Welch HG, Wennberg DE. Hospital volume and surgical mortality in the United States. *N Engl J Med*. 2002;346:1128–1137.
2. Lapar DJ, Mery CM, Kozower BD, Kern JA, Kron IL, Stukenborg GJ, Ailawadi G. The effect of surgeon volume on mortality for off-pump coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2012;143:854–863.
3. Kim LK, Looser P, Swaminathan RV, Minutello RM, Wong SC, Girardi L, Feldman DN. Outcomes in patients undergoing coronary artery bypass graft surgery in the United States based on hospital volume, 2007 to 2011. *J Thorac Cardiovasc Surg*. 2016;151:1686–1692.
4. Catarino PA, Black E, Taggart DP. Why do UK cardiac surgeons not perform their first choice operation for coronary artery bypass graft? *Heart*. 2002;88:643–644.
5. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.
6. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M. Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in metaanalysis. 2000. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed May 7, 2017.
7. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. 2007;8:16.
8. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557.
9. Lonjon G, Boutron I, Trinquart L, Ahmad N, Aim F, Nizard R, Ravaud P. Comparison of treatment effect estimates from prospective nonrandomized studies with propensity score analysis and randomized controlled trials of surgical procedures. *Ann Surg*. 2014;259:18–25.
10. Stram DO. Meta-analysis of published data using a linear mixed-effects model. *Biometrics*. 1996;52:536–544.
11. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
12. Viechtbauer W, Viechtbauer MW. Package "metafor." https://cran.r-project.org/web/packages/metafor/metafor.pdf. Accessed May 7, 2017.
13. Schwarzer G, Schwarzer MG. Package "meta." *Meta-Anal R*. https://cran.r-project.org/web/packages/meta/meta.pdf. Accessed May 7, 2017.
14. Benedetto U, Amrani M, Gaer J, Bahrami T, de Robertis F, Simon AR, Raja SG; Harefield Cardiac Outcomes Research Group. The influence of bilateral internal mammary arteries on short- and long-term outcomes: a propensity score matching in accordance with current recommendations. *J Thorac Cardiovasc Surg*. 2014;148:2699–2705.
15. Buxton BF, Komeda M, Fuller JA, Gordon I. Bilateral internal thoracic artery grafting may improve outcome of coronary artery surgery: risk-adjusted survival. *Circulation*. 1998;98:II1–II6.
16. Calafiore AM, Di Giammarco G, Teodori G, Di Mauro M, Iacolacò AL, Bivona A, Contini M, Vitolla G. Late results of first myocardial revascularization in multiple vessel disease: single versus bilateral internal mammary artery with or without saphenous vein grafts. *Eur J Cardiothorac Surg*. 2004;26:542–548.
17. Carrier M, Cossette M, Pellerin M, Hébert Y, Bouchard D, Cartier R, Demers P, Jeanmart H, Pagé P, Perrault LP. Statin treatment equalizes long-term survival between patients with single and bilateral internal thoracic artery grafts. *Ann Thorac Surg*. 2009;88:789–795.
18. Danzer D, Christenson JT, Kalangos A, Khatchatourian G, Bednarkiewicz M, Faidutti B. Impact of double internal thoracic artery grafts on long-term outcomes in coronary artery bypass grafting. *Tex Heart Inst J*. 2001;28:89.
19. Dewar LR, Jamieson WE, Janusz MT, Adeli-Sardo M, Germann E, MacNab JS, Tyers GFO. Unilateral versus bilateral internal mammary revascularization. *Circulation*. 1995;92:8–13.
20. Elmistekawy EM, Gawad N, Bourke M, Mesana T, Boodhwani M, Rubens FD. Is bilateral internal thoracic artery use safe in the elderly? *J Card Surg*. 2012;27:1–5.
21. Endo M, Nishida H, Tomizawa Y, Kasanuki H. Benefit of bilateral over single internal mammary artery grafts for multiple coronary artery bypass grafting. *Circulation*. 2001;104:2164–2170.
22. Gansera B, Günzinger R, Eichinger W, Neumaier P, Breuer M, Kemkes BM. End of the millenium—end of the single thoracic artery graft? Two thoracic arteries—standard for the next millenium? Early clinical results and analysis of risk factors in 1,487 patients with bilateral internal thoracic artery grafts. *Thorac Cardiovasc Surg*. 2001;49:10–15.
23. Gansera B, Loef A, Angelis I, Gillrath G, Schmidtler F, Kemkes BM. Double thoracic artery—halved mid-term mortality? *Z Kardiol*. 2004;93:878–883.
24. Grau JB, Johnson CK, Kuschner CE, Ferrari G, Shaw RE, Brizzio ME, Zapolanski A. Impact of pump status and conduit choice in coronary artery bypass: a 15-year follow-up study in 1412 propensity-matched patients. *J Thorac Cardiovasc Surg*. 2015;149:1027–1033.
25. Hirotani T, Nakamichi T, Munakata M, Takeuchi S. Risks and benefits of bilateral internal thoracic artery grafting in diabetic patients. *Ann Thorac Surg*. 2003;76:2017–2022.
26. Ioannidis JP, Galanos O, Katritsis D, Connery CP, Drossos GE, Swistel DG, Anagnostopoulos CE. Early mortality and morbidity of bilateral versus single internal thoracic artery revascularization: propensity and risk modeling. *J Am Coll Cardiol*. 2001;37:521–528.
27. Itoh S, Kimura N, Adachi H, Yamaguchi A. Is bilateral internal mammary arterial grafting beneficial for patients aged 75 years or older? *Circ J*. 2016;80:1756–1763.
28. Johnson WD, Brenowitz JB, Kayser KL. Factors influencing long-term (10-year to 15-year) survival after a successful coronary artery bypass operation. *Ann Thorac Surg*. 1989;48:19–25.
29. Jones JW, Schmidt SE, Miller CC III, Beall AC Jr, Baldwin JC. Bilateral internal thoracic artery operations in the elderly. *J Cardiovasc Surg (Torino)*. 2000;41:165.
30. Joo H-C, Youn Y-N, Yi G, Chang B-C, Yoo K-J. Off-pump bilateral internal thoracic artery grafting in right internal thoracic artery to right coronary system. *Ann Thorac Surg*. 2012;94:717–724.
31. Kelly R, Buth KJ, Légaré J-F. Bilateral internal thoracic artery grafting is superior to other forms of multiple arterial grafting in providing survival benefit after coronary bypass surgery. *J Thorac Cardiovasc Surg*. 2012;144:1408–1415.
32. Kinoshita T, Asai T, Suzuki T. Off-pump bilateral skeletonized internal thoracic artery grafting in patients with chronic kidney disease. *J Thorac Cardiovasc Surg*. 2015;150:315–321.
33. Konstanty-Kalandyk J, Piatek J, Rudzinski P, Wrobel K, Bartus K, Sadowski J. Clinical outcome of arterial myocardial revascularization using bilateral internal thoracic arteries in diabetic patients: a single centre experience. *Interact Cardiovasc Thorac Surg*. 2012;15:979–983.
34. Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M, Ebra G. Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups. *Ann Thorac Surg*. 2010;90:101–108.
35. Locker C, Schaff HV, Dearani JA, Joyce LD, Park SJ, Burkhart HM, Suri RM, Greason KL, Stulak JM, Li Z, Daly RC. Multiple arterial grafts improve late survival of patients undergoing coronary artery bypass graft surgery: analysis of 8622 patients with multivessel disease. *Circulation*. 2012;126:1023–1030.
36. Lytle BW, Blackstone EH, Sabik JF, Houghtaling P, Loop FD, Cosgrove DM. The effect of bilateral internal thoracic artery grafting on survival during 20 postoperative years. *Ann Thorac Surg*. 2004;78:2005–2014.
37. Medalion B, Mohr R, Ben-Gal Y, Nesher N, Kramer A, Eliyahu S, Pevni D. Arterial coronary artery bypass grafting is safe and effective in elderly patients. *J Thorac Cardiovasc Surg*. 2015;150:607–612.
38. Mohammadi S, Kalavrouziotis D, Cresce G, Dagenais F, Dumont E, Charbonneau E, Voisine P. Bilateral internal thoracic artery use in patients with low ejection fraction: is there any additional long-term benefit? *Eur J Cardiothorac Surg*. 2014;46:425–431.
39. Naunheim KS, Barner HB, Fiore AC. 1990: Results of internal thoracic artery grafting over 15 years: single versus double grafts: 1992 update. *Ann Thorac Surg*. 1992;53:716–718.
40. Navia DO, Vrancic M, Piccinini F, Camporrotondo M, Dorsa A, Espinoza J, Benzadon M, Camou J. Myocardial revascularization exclusively with bilateral internal thoracic arteries in T-graft configuration: effects on late survival. *Ann Thorac Surg*. 2016;101:1775–1781.
41. Parsa CJ, Shaw LK, Rankin JS, Daneshmand MA, Gaca JG, Milano CA, Glower DD, Smith PK. Twenty-five-year outcomes after multiple internal thoracic artery bypass. *J Thorac Cardiovasc Surg*. 2013;145:970–975.

42. Pettinari M, Sergeant P, Meuris B. Bilateral internal thoracic artery grafting increases long-term survival in elderly patients. *Eur J Cardiothorac Surg*. 2014;47:703–709.

43. Pusca SV, Kilgo PD, Vega JD, Cooper WA, Vassiliades TA, Chen EP, Lattouf OM, Guyton RA, Puskas JD. Propensity-score analysis of early outcomes after bilateral versus single internal thoracic artery grafting. *Innovations (Phila)*. 2008;3:19–24.

44. Rosenblum JM, Harskamp RE, Hoedemaker N, Walker P, Liberman HA, de Winter RJ, Vassiliades TA, Puskas JD, Halkos ME. Hybrid coronary revascularization versus coronary artery bypass surgery with bilateral or single internal mammary artery grafts. *J Thorac Cardiovasc Surg*. 2016;151: 1081–1089.

45. Stevens LM, Carrier M, Perrault LP, Hebert Y, Cartier R, Bouchard D, Fortier A, El-Hamamsy I, Pellerin M. Single versus bilateral internal thoracic artery grafts with concomitant saphenous vein grafts for multivessel coronary artery bypass grafting: effects on mortality and event-free survival. *J Thorac Cardiovasc Surg*. 2004;127:1408–1415.

46. Tarelli G, Mantovani V, Maugeri R, Chelazzi P, Vanoli D, Grossi C, Ornaghi D, Panisi P, Sala A. Comparison between single and double internal mammary artery grafts: results over ten years. *Ital Heart J*. 2001;2:423–427.

47. Walkes J-CM, Earle N, Reardon MJ, Glaeser DH, Wall MJ, Huh J, Jones JW, Soltero ER. Outcomes in single versus bilateral internal thoracic artery grafting in coronary artery bypass surgery. *Curr Opin Cardiol*. 2002;17:598–601.

48. Taggart DP, Altman DG, Gray AM, Lees B, Gerry S, Benedetto U, Flather M. Randomized trial of bilateral versus single internal-thoracic-artery grafts. *N Engl J Med*. 2016;375:2540–2549.

49. Glineur D, Boodhwani M, Hanet C, de Kerchove L, Navarra E, Astarci P, Noirhomme P, El Khoury G. Bilateral internal thoracic artery configuration for coronary artery bypass surgery. *Circ Cardiovasc Interv*. 2016;9:e003518.

Supplemental Material

Table S1. MOOSE Checklist for Meta-analyses of Observational Studies.

Item No	Recommendation	Page No.
	Reporting of background should include	
1	Problem definition	3
2	Hypothesis statement	3
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	4
5	Type of study designs used	4
6	Study population	4
	Reporting of search strategy should include	
7	Qualifications of searchers (e.g., librarians and investigators)	4
8	Search strategy, including time period included in the synthesis and key words	4
9	Effort to include all available studies, including contact with authors	4
10	Databases and registries searched	4
11	Search software used, name and version, including special features used (e.g., explosion)	4
12	Use of hand searching (e.g., reference lists of obtained articles)	4
13	List of citations located and those excluded, including justification	4
14	Method of addressing articles published in languages other than English	4
15	Method of handling abstracts and unpublished studies	4
16	Description of any contact with authors	4
	Reporting of methods should include	
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	4
18	Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)	4
19	Documentation of how data were classified and coded (e.g., multiple raters, blinding and interrater reliability)	4
20	Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate)	4
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	4
22	Assessment of heterogeneity	7
23	Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	5-8

24	Provision of appropriate tables and graphics	See tables and figures
	Reporting of results should include	
25	Graphic summarizing individual study estimates and overall estimate	See figures
26	Table giving descriptive information for each study included	See tables
27	Results of sensitivity testing (e.g., subgroup analysis)	9-10
28	Indication of statistical uncertainty of findings	9-10
29	Quantitative assessment of bias (e.g., publication bias)	9-10
30	Justification for exclusion (e.g., exclusion of non-English language citations)	Figure 1
31	Assessment of quality of included studies	Suppl. Table 2
	Reporting of conclusions should include	
32	Consideration of alternative explanations for observed results	13
33	Generalization of the conclusions (i.e., appropriate for the data presented and within the domain of the literature review)	11-13
34	Guidelines for future research	13
35	Disclosure of funding source	14

Data derived from Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283:2008-2012. Transcribed from the original paper within the NEUROSURGERY® Editorial Office, Atlanta, GA, United States. August 2012.

Table S2. Summary of critical appraisal of included studies using the Newcastle-Ottawa Scale for Cohort Studies.

Study	Selection	Comparability	Outcome/Exposure
Benedetto[1]	****	**	***
Buxton[2]	****	**	***
Calafiore[3]	****	**	***
Carrier[4]	****	**	***
Danzer[5]	****	**	**
Dewar[6]	****	**	*
Elmistekawy[7]	****	**	*
Endo[8]	****	**	***
Gansera 2001[9]	****	**	*
Gansera 2004[10]	****	**	**
Grau[11]	****	**	***
Hirotani[12]	****	*	**
Ioannidis[13]	****	**	*
Itoh[14]	****	**	***
Johnson[15]	****	**	***
Jones[16]	****	*	***
Joo[17]	****	**	***
Kelly[18]	****	**	**
Kinoshita[19]	****	**	***
Konstanty[20]	****	**	*
Kurlansky[21]	****	**	***
Locker[22]	****	**	***
Lytle[23]	****	**	***
Medalion[24]	****	**	***
Mohammadi[25]	****	**	***
Naunheim[26]	****	**	***
Navia[27]	****	**	***
Parsa[28]	****	**	***
Pettinari[29]	****	**	***
Pusca[30]	****	**	*
Rosenblum[31]	****	**	***
Stevens[32]	****	**	***
Tarelli[33]	****	**	***
Walkes[34]	****	**	*

Selection

1) Representativeness of intervention cohort - a) truly representative of the average in the community, treated with CSF drainage during/after thoracic/thoracoabdominal surgery*; b) somewhat representative of the average, treated with CSF drainage during/after thoracic/thoracoabdominal surgery*; c) only selected group of users; d) no description of the derivation of the cohort.
2) Selection of non-intervention cohort – a) drawn from same community as intervention cohort*; b) drawn from a different source; c) no description of the derivation of the non-exposed cohort.
3) Ascertainment of exposure - a) secure record*; b) structured interview*; c) written self-report; d) no description.
4) Demonstration that outcome of interest was not present at start of study - a) yes*; b) no.

Comparability

1) Comparability of cohorts on the basis of the design or analysis - a) study controls for age, and gender*; b) study controls for any additional factor***.**

Outcome

1) Assessment of outcome - a) independent blind assessment***;** b) record linkage*; c) self-report; d) no description.
2) Was follow-up long enough for outcomes to occur - a) yes*; b) no
3) Adequacy of follow up of cohorts - a) complete follow up***;** b) subjects lost to follow up unlikely to introduce bias - < 20 % lost follow up***;** c) follow up rate < 80% and no description of those lost; d) no statement.

Table S3. Risk factor distribution in the populations of the studies included in the primary analysis.

Study		Age (y) Mean±SD	Female (%)	DM (%)	EF	COPD (%)	Mean #of grafts/anastomosis per patient	Use of sequential grafting	Use of skeletonized ITAs	Mean #of CABG performed per year
Benedetto[1]		NR (Ranges)	10.8	15.9	EF<50% in 13.2%	7.7	2.88 (BITA) vs 2.74 (SITA)	NO	YES	347,17
Buxton[2]		58.6 ± 9	10.6	6.8	EF<50% in 4.9%	NR	3.38±0.80 (BITA) vs 3.07±0.89 (SITA)	YES	NO	258,87
Calafiore[3]		60.7 ± 8.3	19.3	24.2	59.4 ± 13.1	2.8	2.8±0.9 (BITA) vs 2.8±0.9 (SITA)*	YES	YES	120,91
Carrier[4]		61 ± 9	16	21	NR	NR	NR	YES	NO	515,23
Danzer[5]		59.8 ± 8.8	12	13.6	EF<40% in 13.6	NR	NR	NO	NO	115,78
Dewar[6]		NR	15.4	17.7	NR	NR	3.9 (BITA) vs 3.57 (SITA)	NO	NR	128,07
Elmistekawy[7]		71.2 ± 5.0	23.4	32.7	NR	NR	2.93±0.63 (BITA) vs 2.86±0.78 (SITA)	NO	YES	411,13
Endo[8]		61 (6-85)	9.7	42.9	54% (median)	NR	2.85 (BITA) vs 2.66 (SITA)	YES	YES	87,56
Gansera 2001[9]		64.4± 9.4	18.6	28.1	62.1 ± 14.6	NR	3.63±0.9 (BITA) vs 3.14±0.9 (SITA)	NO	NO	937,28
Gansera 2004[10]		69.2 (42.7-88.6)	16	26	NR	NR	3.58 (BITA) vs 3.13 (SITA)	NO	NO	533,42
Grau[11]		60 ± 9	10.4	11	51 ± 11	5.1	3.7±1 (BITA off-pump), 3.5±1 (BITA on-pump), 3.5±1 (SITA off-pump), 3.4±1 (SITA on-pump)*	Surgical details NR	NR	334,69
Hirotani[12]		64.8 ± 7.8	23	100	48.2 ± 15.1	NR	3.5±1.0 (BITA) vs 2.8±1.0 (SITA)	YES	NO	25,79
Ioannidis[13]		62.0±10.3	22.6	25.6	46.5 ± 13.7	13	NR	Surgical details NR	NR	433,28
Itoh[14]		77.6 ± 2.5	23.4	37.4	EF<40% in 10.3%	NR	NR	NO	YES	16,11
Johnson[15]		NR	NR	NR	NR	NR	NR	Surgical details NR	NR	145,59
Jones[16]		69.2	19.2	NR	EF<50% in 38.9%	NR	3.34 (BITA) vs 2.90 (SITA)	NO	NR	51,00
Joo[17]		60.4 ± 9.1	39.8	38.3	57 ± 11%	7.4	3.22±0.78 (SITA) vs 3.32±0.69 (BITA)*	YES	semi-skeletonized method used	176,37
Kelly[18]		58.4 ± 10.0	18	26	EF<40% in 7%	11	3.2±1.0 (BITA) vs 3.2±0.9 (SITA)	YES	NO	511,71
Kinoshita[19]		69 ± 8	16	61	52 ± 14%	19	NR	YES	YES	96,89
Konstanty[20]		62 ± 8.3	34	60.5	51.6 ± 8	7.8	2.60 ± 0.59 (BITA) vs 2.57±0.61 (SITA)	NO	NO	58,80
Kurlansky[21]		62.9 ± 10.0	14.9	20.8	EF<30% in 3.9%	NR	Total #of grafts: 3.3 (BITA) vs 3.1 (SITA)	YES	YES	206,02
Locker[22]		NR	NR	NR	NR	NR	NR	YES	YES	490,34
Lytle[23]		57.5 ± 8.1	12	12	NR	NR	NR	Surgical details NR	NR	535,19
Medalion[24]		NR (ranges)	27	32.2	EF≤30% in 8.2%	5.5	NR	YES	YES	125,96
Mohammadi[25]		54.6 ± 9.5	9.3	14	EF≤30% in 30.2%	12.4	3.7±1.0 (BITA) vs 3.6±1.0 (SITA)	NO	NO	87,56

Naunheim[26]		49.6 ± 7.9	17	4	NR	NR	2.4±0.5 (BITA) vs 2.3±0.8 (SITA)	NO	NO	93,19
Navia[27]		63.7 ± 9.1	9.8	25.9	NR	4.2	NR	YES	YES	142,06
Parsa[28]		59 (median)	19.8	14.7	51% (median)	3.9	Median #of grafts per patients: 3 (BITA) vs 3 (SITA)	YES	NR	679,45
Pettinari[29]		73.2 ± 2.8	26.1	12.6	44.3 ± 32.2	16.3	3.14±0.92 (BITA) vs 3.07±0.93 (SITA)*	NO	semi-skeletonized method used	100,12
Pusca[30]		58.0 ± 0.34	17.4	25.2	51.6± 11.4	12	3.67 (BITA) vs 3.45 (SITA)	NO	YES	1148,07
Rosenblum[31]		59.0 ± 10.1	15.5	27.6	52.2 ± 11.0	1.8	3.7±1.0 (BITA) vs 3.3±0.9 (SITA)	NO	NO	832,34
Stevens[32]		57 ± 9	12	12	NR	4	3.4±0.6 (BITA) vs 3.2±0.5 (SITA)	NO	NO	434,58
Tarelli[33]		56.5 ± 8.2	7.3	11.3	57.2 ± 13.6	NR	3.0±0.6 (BITA) vs 2.9±0.5 (SITA)	NO	NO	102,86
Walkes[34]		57.0 ± 9.4	1.9	29.5	NR	24.1	2.99±0.88 (BITA) vs 2.90±0.91 (SITA)	NO	NO	107,80

*data available for matched populations only. COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EF, ejection fraction; NR, not reported; SD, standard deviation.

Figure S1. The “Leave-one-out” analysis for the primary outcome.

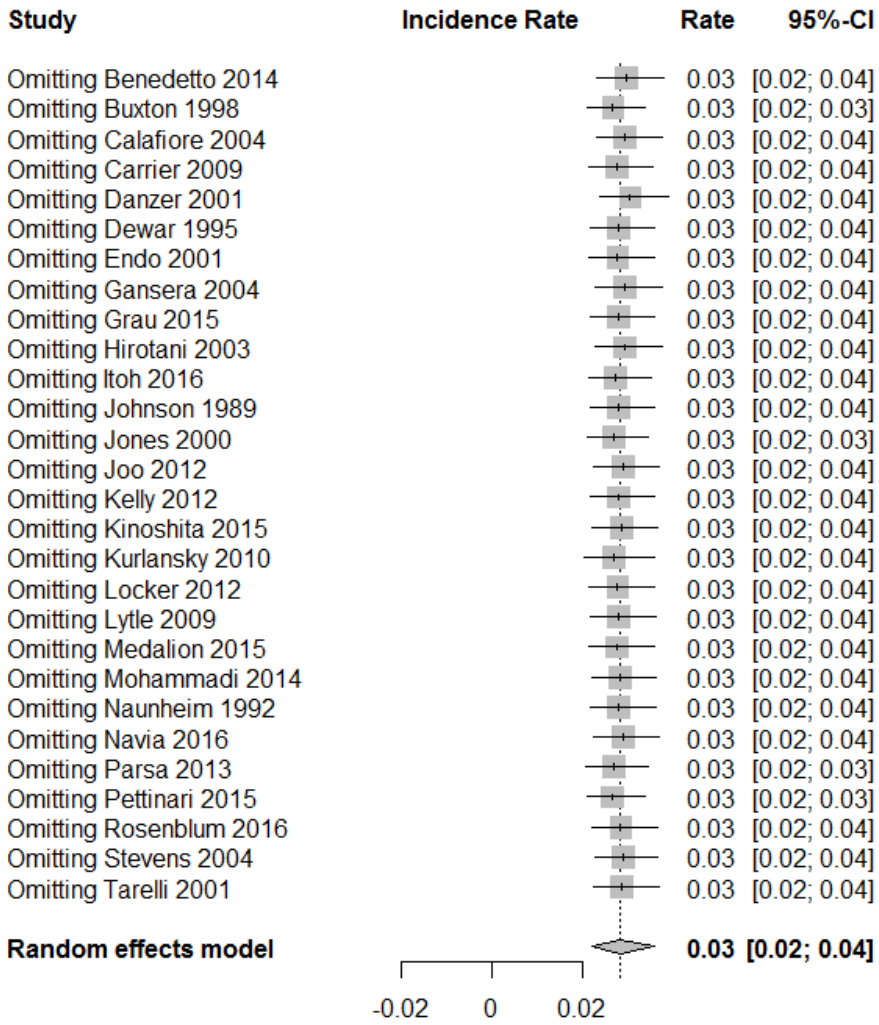
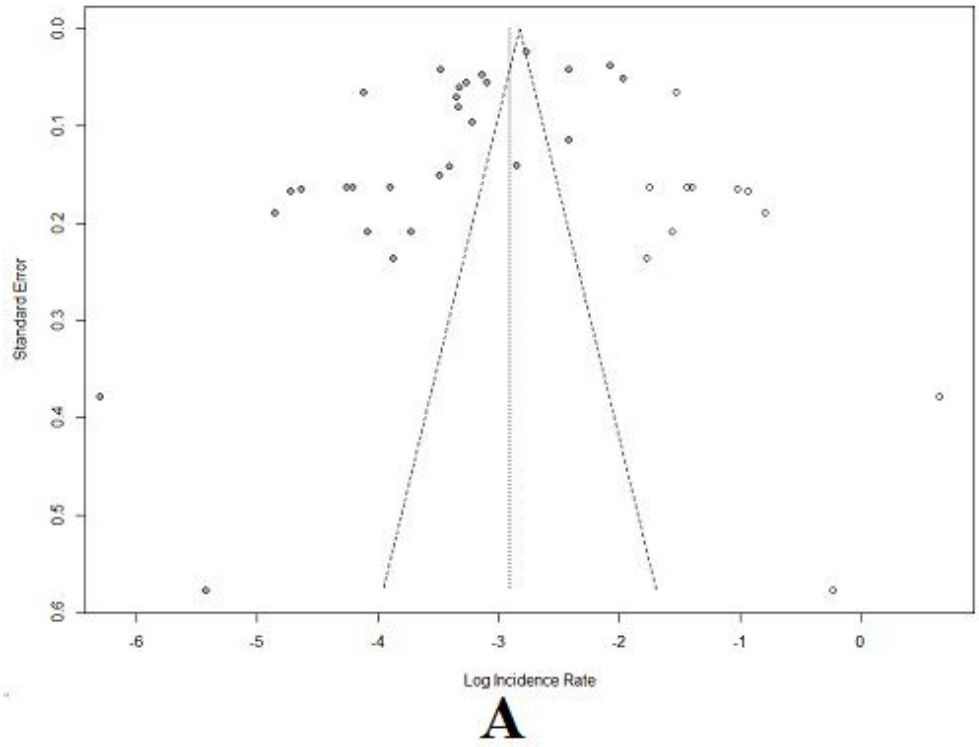
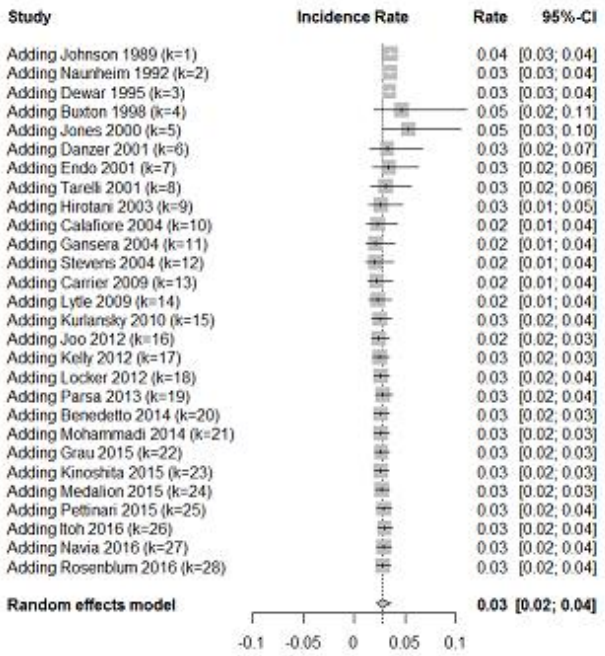


Figure S2. The pooled analysis for long term mortality: A) Funnel plot with trim and fill method and B) Cumulative meta-analysis.



A



B

Figure S3. The pairwise comparison for long term mortality among the adjusted studies using the incident rate ratio.

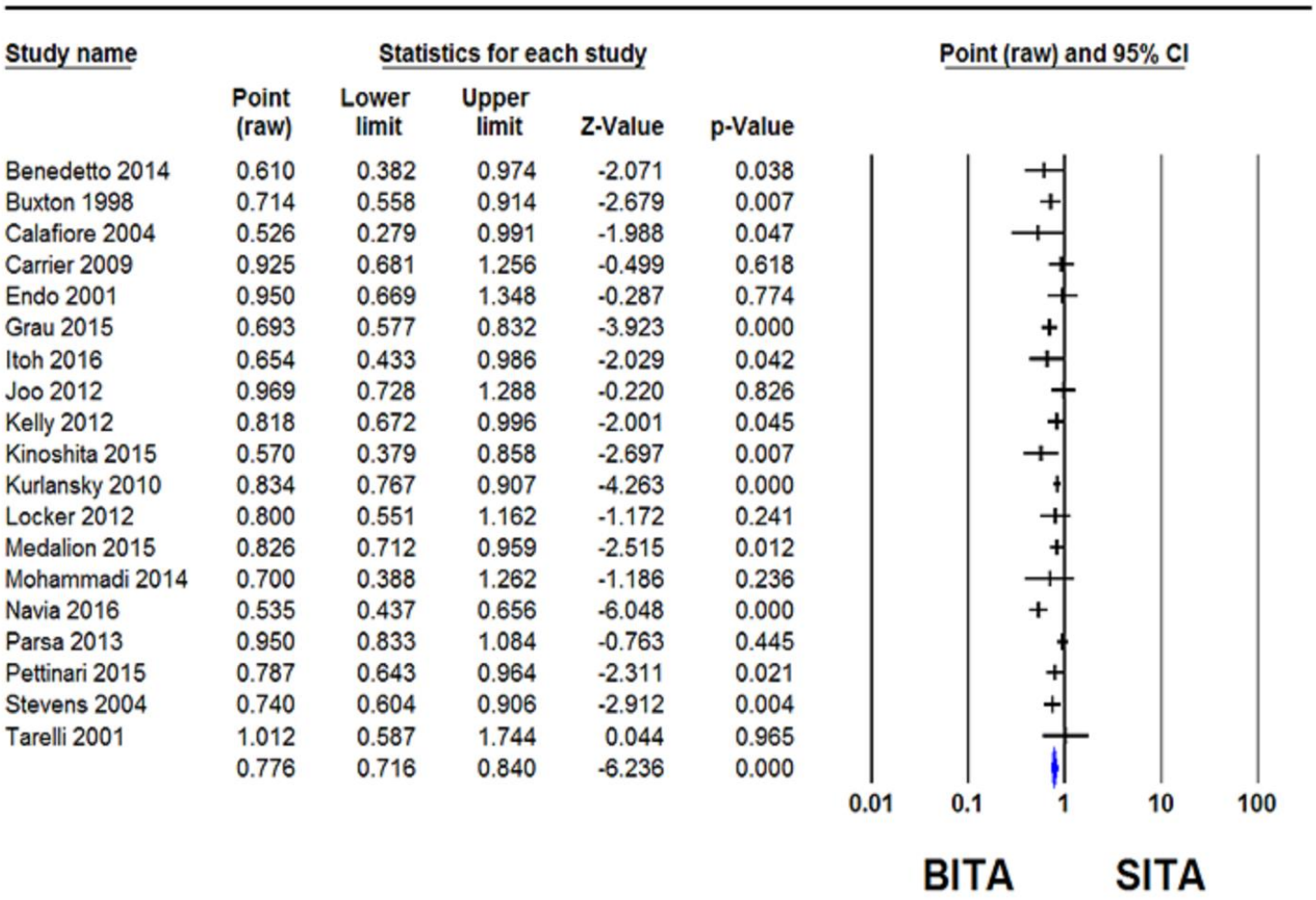


Figure S4. The effect of the percentage of BITA use on the pooled event rate of A) peri-operative myocardial infarction, B) peri-operative stroke, C) major postoperative adverse events (MAE), D) operative mortality.

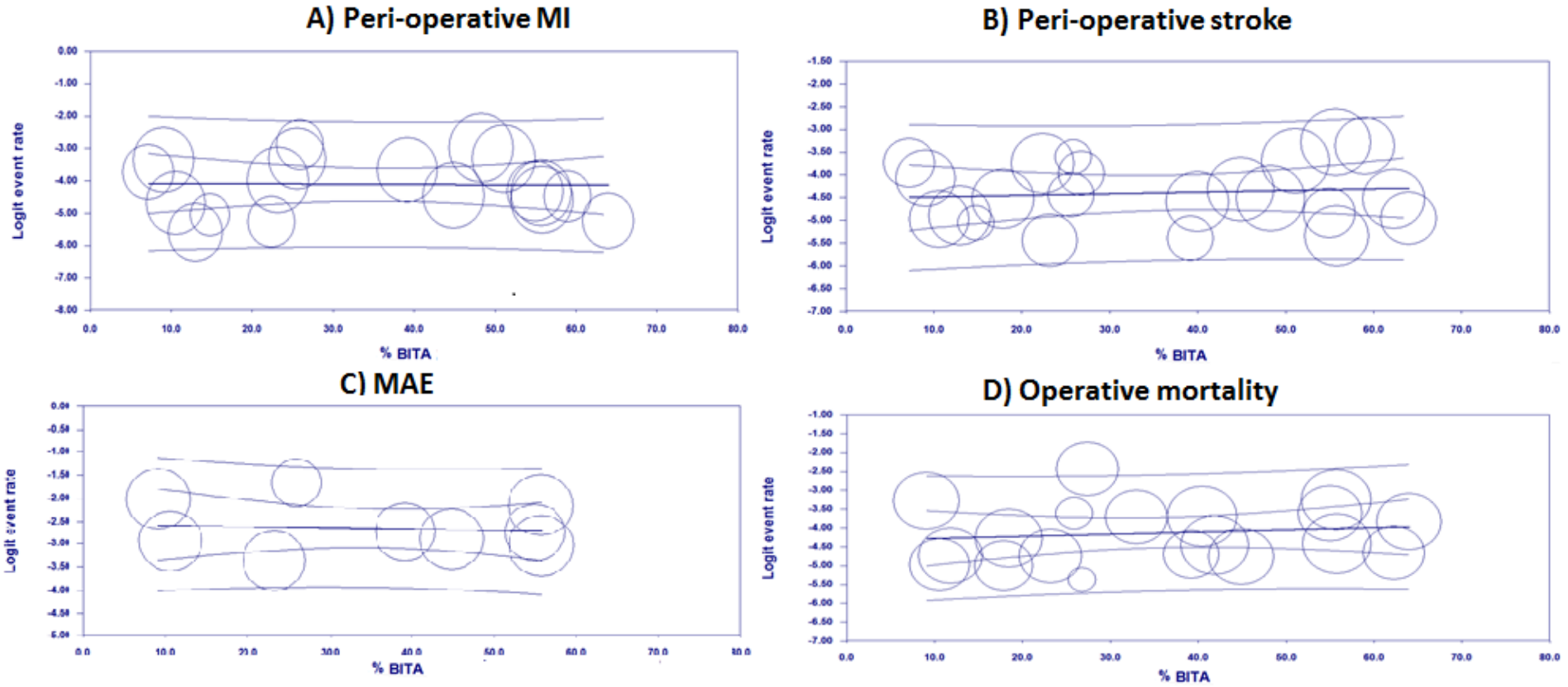
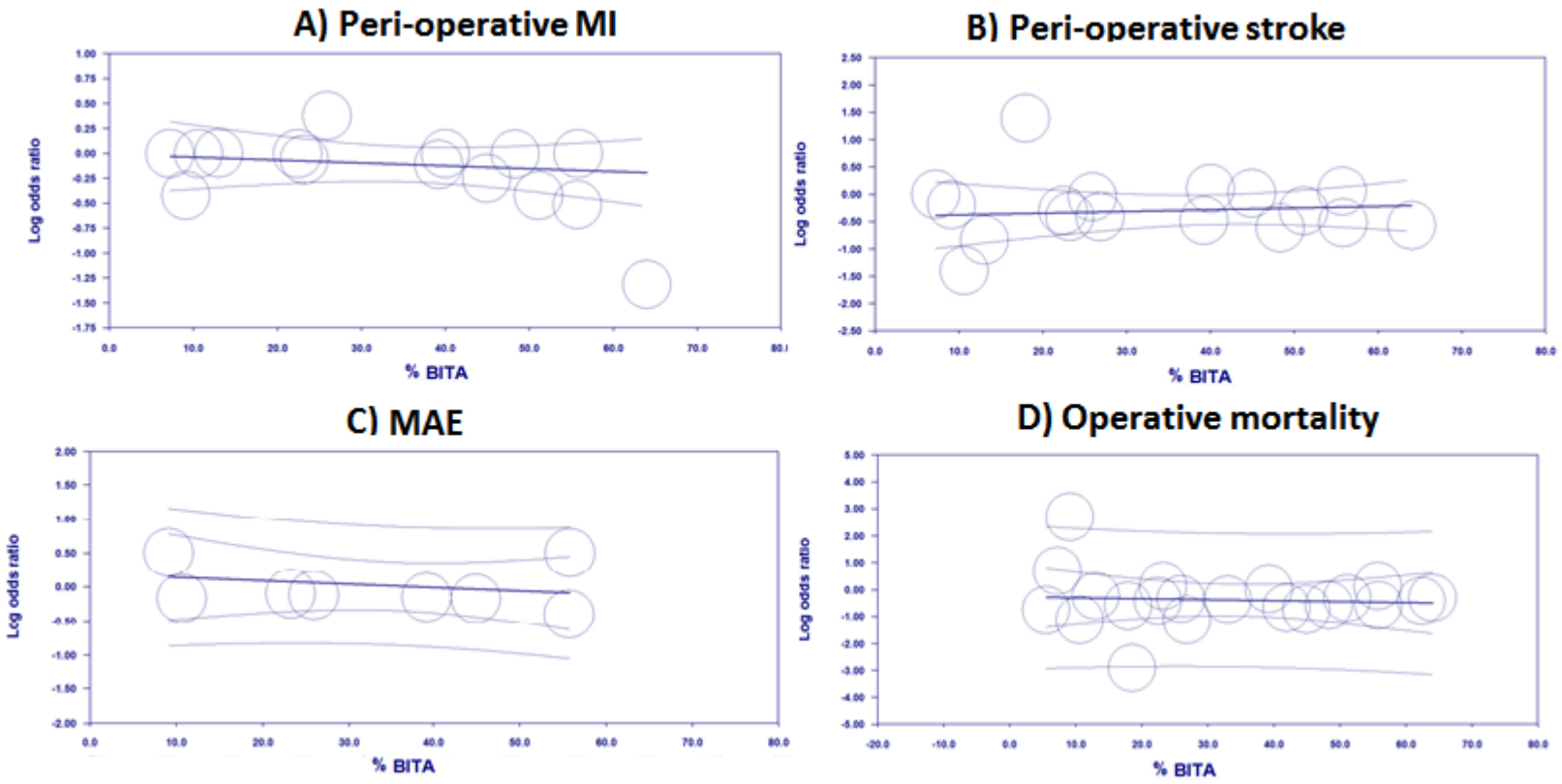


Figure S5. The effect of the percentage of BITA use on the odds ratio of A) peri-operative myocardial infarction, B) peri-operative stroke, C) major postoperative adverse events (MAE), D) operative mortality.



Supplemental References:

1. Benedetto U, Amrani M, Gaer J, Bahrami T, de Robertis F, Simon AR, Raja SG, Group HCOR, others. The influence of bilateral internal mammary arteries on short-and long-term outcomes: a propensity score matching in accordance with current recommendations. *J Thorac Cardiovasc Surg.* 2014;148:2699–2705.

2. Buxton BF, Komeda M, Fuller JA, Gordon I. Bilateral internal thoracic artery grafting may improve outcome of coronary artery surgery. Risk-adjusted survival. *Circulation.* 1998;98:II1–6.

3. Calafiore AM, Di Giammarco G, Teodori G, Di Mauro M, Iacoìacò AL, Bivona A, Contini M, Vitolla G. Late results of first myocardial revascularization in multiple vessel disease: single versus bilateral internal mammary artery with or without saphenous vein grafts. *Eur J Cardiothorac Surg.* 2004;26:542–548.

4. Carrier M, Cossette M, Pellerin M, Hébert Y, Bouchard D, Cartier R, Demers P, Jeanmart H, Pagé P, Perrault LP. Statin treatment equalizes long-term survival between patients with single and bilateral internal thoracic artery grafts. *Ann Thorac Surg.* 2009;88:789–795.

5. Danzer D, Christenson JT, Kalangos A, Khatchatourian G, Bednarkiewicz M, Faidutti B. Impact of double internal thoracic artery grafts on long-term outcomes in coronary artery bypass grafting. *Tex Heart Inst J*. 2001;28:89.

6. Dewar LR, Jamieson WE, Janusz MT, Adeli-Sardo M, Germann E, MacNab JS, Tyers GFO. Unilateral versus bilateral internal mammary revascularization. *Circulation*. 1995;92:8–13.

7. Elmistekawy EM, Gawad N, Bourke M, Mesana T, Boodhwani M, Rubens FD. Is bilateral internal thoracic artery use safe in the elderly? *J Card Surg.* 2012;27:1–5.

8. Endo M, Nishida H, Tomizawa Y, Kasanuki H. Benefit of bilateral over single internal mammary artery grafts for multiple coronary artery bypass grafting. *Circulation.* 2001;104:2164–2170.

9. Gansera B, Günzinger R, Eichinger W, Neumaier P, Breuer M, Kemkes BM, others. End of the millenium–end of the single thoracic artery graft? Two thoracic arteries–standard for the next millenium? Early clinical results and analysis of risk factors in 1,487 patients with bilateral internal thoracic artery grafts. *Thorac Cardiovasc Surg.* 2001;49:10–15.

10. Gansera B, Loef A, Angelis I, Gillrath G, Schmidtler F, Kemkes BM. Double thoracic artery—halved mid-term mortality? *Z Für Kardiologie.* 2004;93:878–883.

11. Grau JB, Johnson CK, Kuschner CE, Ferrari G, Shaw RE, Brizzio ME, Zapolanski A. Impact of pump status and conduit choice in coronary artery bypass: A 15-year follow-up study in 1412 propensity-matched patients. *J Thorac Cardiovasc Surg.* 2015;149:1027–1033.

12. Hirotani T, Nakamichi T, Munakata M, Takeuchi S. Risks and benefits of bilateral internal thoracic artery grafting in diabetic patients. *Ann Thorac Surg*. 2003;76:2017–2022.

13. Ioannidis JP, Galanos O, Katritsis D, Connery CP, Drossos GE, Swistel DG, Anagnostopoulos CE. Early mortality and morbidity of bilateral versus single internal thoracic artery revascularization: propensity and risk modeling. *J Am Coll Cardiol.* 2001;37:521–528.

14. Itoh S, Kimura N, Adachi H, Yamaguchi A. Is bilateral internal mammary arterial grafting beneficial for patients aged 75 years or older? *Circ J.* 2016;80:1756–1763.

15. Johnson WD, Brenowitz JB, Kayser KL. Factors influencing long-term (10-year to 15-year) survival after a successful coronary artery bypass operation. *Ann Thorac Surg.* 1989;48:19–25.

16. Jones JW, Schmidt SE, Miller III CC, Beall Jr AC, Baldwin JC. Bilateral internal thoracic artery operations in the elderly. *J Cardiovasc Surg (Torino).* 2000;41:165.

17. Joo H-C, Youn Y-N, Yi G, Chang B-C, Yoo K-J. Off-pump bilateral internal thoracic artery grafting in right internal thoracic artery to right coronary system. *Ann Thorac Surg.* 2012;94:717–724.

18. Kelly R, Buth KJ, Légaré J-F. Bilateral internal thoracic artery grafting is superior to other forms of multiple arterial grafting in providing survival benefit after coronary bypass surgery. *J Thorac Cardiovasc Surg*. 2012;144:1408–1415.

19. Kinoshita T, Asai T, Suzuki T. Off-pump bilateral skeletonized internal thoracic artery grafting in patients with chronic kidney disease. *J Thorac Cardiovasc Surg.* 2015;150:315–321.

20. Konstanty-Kalandyk J, Piatek J, Rudzinski P, Wrobel K, Bartus K, Sadowski J. Clinical outcome of arterial myocardial revascularization using bilateral internal thoracic arteries in diabetic patients: a single centre experience. *Interact Cardiovasc Thorac Surg.* 2012;15:979–983.

21. Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M, Ebra G. Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups. *Ann Thorac Surg*. 2010;90:101–108.

22. Locker C, Schaff HV, Dearani JA, Joyce LD, Park SJ, Burkhart HM, Suri RM, Greason KL, Stulak JM, Li Z, Daly RC. Multiple arterial grafts improve late survival of patients undergoing coronary artery bypass graft surgery: analysis of 8622 patients with multivessel disease. *Circulation.* 2012;126:1023–1030.

23. Lytle BW, Blackstone EH, Sabik JF, Houghtaling P, Loop FD, Cosgrove DM. The effect of bilateral internal thoracic artery grafting on survival during 20 postoperative years. *Ann Thorac Surg.* 2004;78:2005–2014.

24. Medalion B, Mohr R, Ben-Gal Y, Nesher N, Kramer A, Eliyahu S, Pevni D. Arterial coronary artery bypass grafting is safe and effective in elderly patients. *J Thorac Cardiovasc Surg.* 2015;150:607–612.

25. Mohammadi S, Kalavrouziotis D, Cresce G, Dagenais F, Dumont E, Charbonneau E, Voisine P. Bilateral internal thoracic artery use in patients with low ejection fraction: is there any additional long-term benefit? *Eur J Cardiothorac Surg.* 2014;46:425–431.

26. Naunheim KS, Barner HB, Fiore AC. 1990: Results of internal thoracic artery grafting over 15 years: single versus double grafts. 1992 update. *Ann Thorac Surg.* 1992;53:716–718.

27. Navia DO, Vrancic M, Piccinini F, Camporrotondo M, Dorsa A, Espinoza J, Benzadon M, Camou J. Myocardial revascularization exclusively with bilateral internal thoracic arteries in T-graft configuration: effects on late survival. *Ann Thorac Surg.* 2016;101:1775–1781.

28. Parsa CJ, Shaw LK, Rankin JS, Daneshmand MA, Gaca JG, Milano CA, Glower DD, Smith PK. Twenty-five-year outcomes after multiple internal thoracic artery bypass. *J Thorac Cardiovasc Surg.* 2013;145:970–975.

29. Pettinari M, Sergeant P, Meuris B. Bilateral internal thoracic artery grafting increases long-term survival in elderly patients. *Eur J Cardiothorac Surg.* 2014;47:703–709.

30. Pusca SV, Kilgo PD, Vega JD, Cooper WA, Vassiliades TA, Chen EP, Lattouf OM, Guyton RA, Puskas JD. Propensity-score analysis of early outcomes after bilateral versus single internal thoracic artery grafting. *Innov Technol Tech Cardiothorac Vasc Surg*. 2008;3:19–24.

31. Rosenblum JM, Harskamp RE, Hoedemaker N, Walker P, Liberman HA, de Winter RJ, Vassiliades TA, Puskas JD, Halkos ME. Hybrid coronary revascularization versus coronary artery bypass surgery with bilateral or single internal mammary artery grafts. *J Thorac Cardiovasc Surg.* 2016;151:1081–1089.

32. Stevens LM, Carrier M, Perrault LP, Hebert Y, Cartier R, Bouchard D, Fortier A, El-Hamamsy I, Pellerin M. Single versus bilateral internal thoracic artery grafts with concomitant saphenous vein grafts for multivessel coronary artery bypass grafting: effects on mortality and event-free survival. *J Thorac Cardiovasc Surg.* 2004;127:1408–1415.

33. Tarelli G, Mantovani V, Maugeri R, Chelazzi P, Vanoli D, Grossi C, Ornaghi D, Panisi P, Sala A. Comparison between single and double internal mammary artery grafts: results over ten years. *Ital Heart J Off J Ital Fed Cardiol.* 2001;2:423–427.

34. Walkes J-CM, Earle N, Reardon MJ, Glaeser DH, Wall MJ, Huh J, Jones JW, Soltero ER, others. Outcomes in single versus bilateral internal thoracic artery grafting in coronary artery bypass surgery. *Curr Opin Cardiol.* 2002;17:598–601.